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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,131	04/01/2002	Yoshio Umezawa	2002-0324A	9485

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,131	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *6-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election without traverse of Group I, claims 1-5 in the response filed 4/20/04 is acknowledged.

Claims 2 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 (upon which Claim 3 depends) is indefinite in the recitation "wherein the polypeptide that binds specifically to cGMP is a cGMP-binding protein" as it is unclear how a "cGMP-binding protein" is more limited in scope than a "polypeptide that binds specifically to cGMP". As such it is unclear how claim 2 further limits claim 1. For purposes of examination Claims 1 and 2 are considered duplicates.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of fusion proteins and method of use thereof for detecting cGMP. The specification

teaches the structure of only five representative species of such fusion protein each of them using only the same specific chromophores and fragment of the same cGMP binding protein or a specific mutant thereof. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of including a cGMP binding protein. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cGMP probe consisting of two chromophores capable of exhibiting FRET and residues 48-671 of cGMP-dependent kinase Iα or the A12 mutant of cGMP-dependent kinase Iα and optionally linker peptides between said chromophores and cGMP binding peptide, does not reasonably provide enablement for any construct comprising two chromophores and a cGMP-binding polypeptide. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim are so broad as to encompass any construct comprising two chromophores and a cGMP-binding polypeptide. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of constructs broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Furthermore, the specification and Honda et al. explicitly show that not all peptides which specifically bind to cGMP can be used in cGMP detection constructs as claimed as many such constructs fail to show the requisite alteration in fluorescence when cGMP is bound. However, in this case the disclosure is limited to five specific constructs which exhibit

the desired property of differential fluorescence when cGMP is bound.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass constructs comprising all modifications and fragments of any cGMP binding polypeptide because the specification does **not** establish: (A) regions of the cGMP binding protein structure which may be modified without effecting cGMP binding ability and/or the property of differential fluorescence when cGMP is bound; (B) the general tolerance of cGMP-visualizing probes to modification and extent of such tolerance; (C) a rational and predictable scheme for

modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any construct comprising two chromophores and a cGMP-binding polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by either of Honda et al. (Reference AO of applicants PTO-1449) or Sato et al. (Reference AN of applicants PTO-1449).

Honda et al. teach fusion constructs consisting of cyan fluorescent protein fused to the N-terminus of several fragments of cGMP-dependent kinase Iα and yellow fluorescent protein fused to the C-terminus thereof and the use of these fusions for the detection of cGMP.

Sato et al. teach fusion constructs consisting of cyan fluorescent protein fused to the N-terminus of a fragment of cGMP-dependent kinase Iα (i.e., residues 48-671) or a mutant of cGMP-dependent kinase Iα in which all leucine, isoleucine and cysteine residues in positions 1-47 were replaced with alanine and yellow fluorescent protein fused to the C-terminus thereof and the use of these fusions for the detection of cGMP.

It is noted that the date of the cited references falls after the filing date of applicants claims foreign priority document, however, applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation

of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsien et al. (US Patent 5,998,204).

Tsien et al. teach fusion constructs consisting of two fluorescent proteins separated by a peptide which binds an analyte of interest and the use of such constructs for the detection of the analyte by monitoring changes in FRET. Tsien et al. teach that the peptide which binds the analyte can be cGMP-dependent protein kinase (see column 2, lines 30-32 and column 11, line 44 - column 12, line 23) and that preferably cyan fluorescent protein (i.e., W1B in Tsien et al.) is fused to the N-terminus and yellow fluorescent protein (i.e., 10C in Tsien et al.) is fused to the C-terminus of the peptide (see column 8, lines 32-38 and Table 1).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter

of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. (US Patent 5,998,204) in view of Zhao et al.

Tsien et al. is described above. They do not specifically teach the use of the described construct in which the peptide which binds the analyte is cGMP-dependent protein kinase for the detection of cGMP. However, Tsien et al. teach that the use of the constructs described is for the detection of an analyte which binds to the peptide within the construct where binding of the analyte to the peptide results in a conformational change of the peptide (see for example column 1, lines 49-65).

Zhao et al. teach that cGMP-dependent protein kinase binds cGMP and induces a marked conformational change upon binding.

Therefore, it would have been obvious to one of to use the construct in which the peptide which binds the analyte is cGMP-dependent protein kinase for the detection of cGMP as the

importance of cGMP levels in a variety of physiological processes is well known in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652